

Immune Profiles of Patients Co-Infected with Soil-Transmitted Helminths and *Mycobacterium tuberculosis*: Implications for Control

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Abstract

Mycobacterium tuberculosis and soil transmitted helminth infections persisted as major public health concern and developmental challenges of the world. Apart from the contribution of co-infection like HIV as a major risk factor for higher tuberculosis mortality rates, the impact of soil transmitted helminth co-infection also requires another consideration. Geographically, both soil transmitted helminthiasis and tuberculosis have a substantial overlap in tropical and subtropical areas of the world which might be due to the contradictory impact of immune response against them. The role of intestinal helminth infection in anti-microbial immunity was evaluated using both cellular phenotype and cytokine profiles in patients with tuberculosis and patients with concomitant infections. Th1 and Th2 cells that act against *Mycobacterium tuberculosis* and soil transmitted helminths cross regulate each other by action of their cytokine production mainly IFN- γ and IL4, respectively. Moreover, de-worming of the helminths also affect the immunogenicity of the only available vaccine against *Mycobacterium tuberculosis*. Few studies were conducted to assess such impacts of helminthiasis on the host immune response against tuberculosis and the efficacy of BCG vaccination implying that the studies as non-consistent and inconclusive. On the contrary, infection with soil transmitted helminths minimizes immune mediated diseases. Therefore, this comprehensive article reviews the immune profiles of co-infection between the two diseases. We also forwarded some better understandings for the control of the diseases in co-endemic geographical settings.

Keywords: Co-Infection; Immune Profile; Soil Transmitted Helminths; *Mycobacterium tuberculosis*

Introduction

Mycobacterium tuberculosis (MTB) is an etiologic agent that causes an air born bacterial disease, tuberculosis. Other members of the *Mycobacterium tuberculosis* complex (MTBC) like *M. bovis*, *M. africanum* and *M. microti* also cause human tuberculosis in addition to animal infection [1]. Despite their close genetic similarity and the same ancestor, these organisms differ considerably with regard to epidemiology, pathogenicity and even on their host spectrum [2]. The bacteria usually enter the host via inhalation of droplets containing viable bacteria and reach the alveolar spaces where they are being ingested by macrophages and dendritic cells [3]. On the other hand, soil transmitted helminths (STH) are also those helminths which include *Ascaris lumbricoides* (roundworms), *Trichuris trichiura* (whipworms) and *Necator americanus* or *Ancylostoma duodenale* (hookworms) that cause ascariasis, trichuriasis and hookworm diseases, respectively.

MTB infects about one-third of the world's population in which only a small proportion (about 5 - 10%) are developing TB through their life time while the rest remained as an asymptomatic. The disease causes a mortality rate of about 1.7 million people in 2016 [4]. Likewise, about 4.5 billion individuals are also exposed to STH globally of which about 2 billion are infected as either in single or poly-parasitized forms. The diseases caused by those agents are more prevalent in underdeveloped countries where food insecurity and poor hygiene are common causing high socio-economic burden.

There are no successfully established immune profile and treatment studies among TB and soil transmitted co-infected patients. Few of the studies made on the co-infection of the two diseases imply that further consideration as to be needed. The way how concurrent MTB and STH worm infections affects the immunity of an individual has also been not elucidated [5]. Furthermore, the impact of intestinal helminth infection on active tuberculosis is not well understood [6]. Thus, understanding the immune response and treatment of TB in such MTB-STH co-infected individuals remained as an open field of study.

Abate [7] also revealed that concurrent infections of helminths with MTB have an impact for activation of chronic MTB infection. However, his study didn't focus on STH which have greater prevalence throughout the world as well as in Ethiopia. The immune profile of IL-4 which impedes production of Th1 from the naïve T cells and makes individuals as more susceptible to TB was also not elucidated by him. The role of IL-12 produced by phagocytic cells and induce Th1 but inhibits Th2 production should also require more detailed studies. A recently discovered pro-inflammatory cytokine IL-18 that induce production of IFN- γ and seems to be protective against TB need to be studied. Over expression of IL-10 in mice increased susceptibility to MTB infection. Contrarily, increased level of the same cytokine (IL-10) is not responsible for failure of Th1 that resolves MTB infection in mice [8]. Those conflicting results in animal model on IL-10 immune profile will also need further study.

Such limited understanding of parasitosis co-morbidities with tuberculosis, the immune response, lack of intervention guidelines for treatment and scarce information on vaccination aggravate their problem. Limitations of knowledge on the immune profile of co-infection between these diseases need more concern for designing proper treatment and control strategies.

Materials and Methods

This review used a total of 46 published scientific papers on tuberculosis, Parasitosis, TB parasitic co-infections and their immune profiles from 1995 to 2017. Journal articles with full text or abstracts in English, WHO reports and other previously written reviews were also my information sources. Soil transmitted helminths, tuberculosis and immune profiles of *MTB*-parasitic co-infections were some of the most commonly used key words or phrases to download articles, reviews and reports.

Results and Discussion

STH - *MTB* Co-infections and their immune profiles

Geographically, soil transmitted helminthiasis and tuberculosis overlap with the impact of one over the other is not yet clearly stated. Pedersen and Fenton [9] showed helminth infections stimulate Th2 immune profile and IgE antibody levels which alter Th1 response necessary for the protection of TB and reactivates even latent TB infections. On the other hand, the impact of Th2 and IgE responses toward the protective immune response of TB is not understood [10]. A study made on animal model (mice) indicated that there were no any immunological effects of chronic helminth infection to exacerbate *MTB* infection [11].

Th1 cells produce IFN- γ and expresses cytotoxicity, activate macrophages and promote cell mediated immunity. On the contrary, the Th2 cells secrete the cytokines IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13, but not induce B cell differentiation with production of all immunoglobulin isotypes including IgE that targets to the worms, and inhibit several macrophage functions [12].

In addition to the shifting of immune background towards Th2 immune responses due to an infection and cross regulation of the T cells (Figure 1), intestinal worms also induce regulatory T cells (Tregs) [13]. Indeed, Tregs are primarily important in the control of pathogenic T cells and autoimmune responses rather than regulating pathogenic microbes [14]. The increase of Treg favors the establishment of mycobacterial infection and the development of active TB disease [15] contrary to their protective role against helminth parasites [16]. They produce inhibitory cytokines (IL-10 and TGF- β) that suppresses Th1 type responses to TB interfering with effector T cell activation. Strong induction of IL-10 in response to intestinal helminth infections plays a pronounced role in immune suppression associated with active TB. Based on the review by Rook., *et al.* [17] further investigation is needed on the impact of these worm-induced Th2 and/or Treg responses for protection against Mycobacterial diseases or for vaccinations against the intracellular pathogens. These are questions of important public health concern remained particularly in the developing world where both of the infections are endemic.

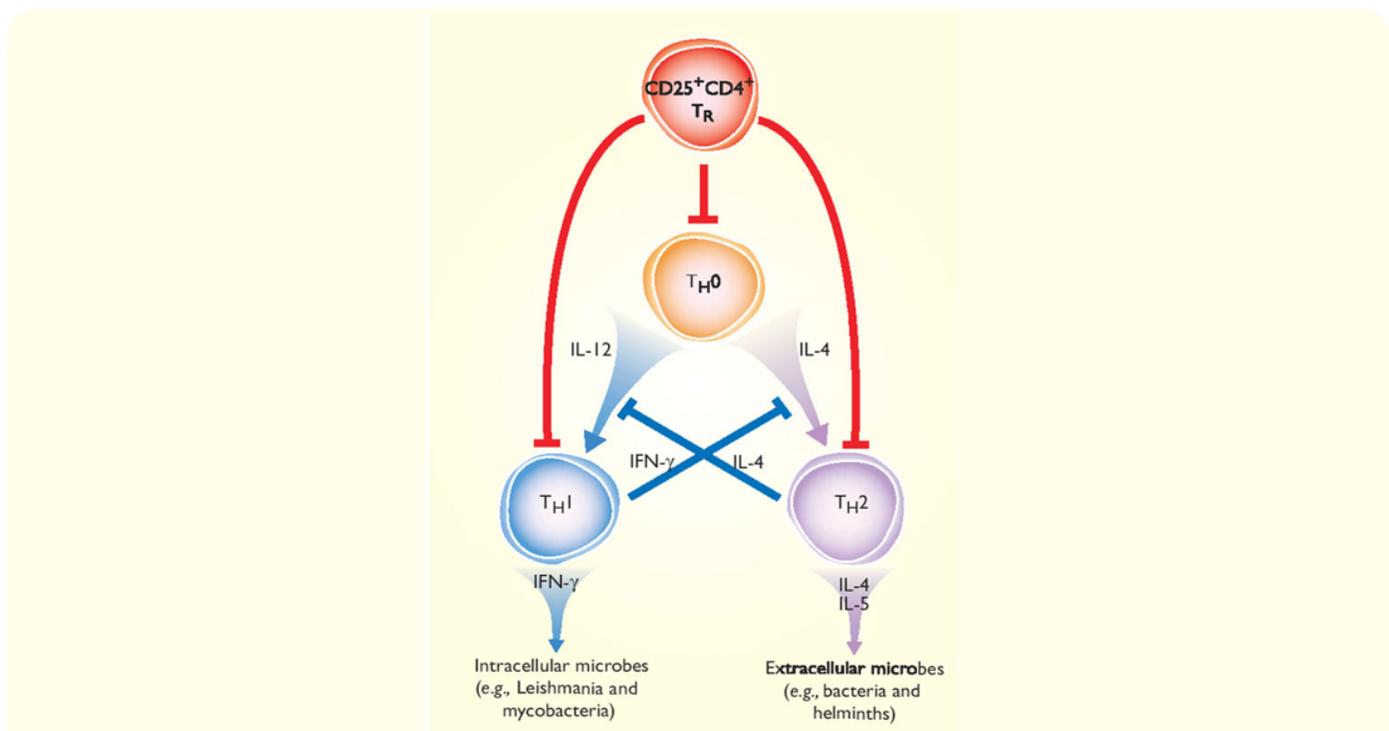


Figure 1: Hierarchy of T cell regulation adopted from Sakaguchi (2003). *T_H1* cells and *T_H2* cells cross-regulate the development of each population from *T_H0* cells via IFN- γ or IL-4, respectively. Naturally arising CD25+CD4+ regulatory T cells suppress the activation and expansion of *T_H0*, *T_H1* and *T_H2* cells, thereby controlling the magnitude and the character of T cell responses. Treg, T regulatory cell.

Resende, *et al.* [6] investigated the role of helminth infections in anti-*MTB* immunity by evaluating both cellular phenotype and cytokine profiles in patients with TB and patients with concomitant TB (TB + Helm) during tuberculosis therapy. The studies revealed that Twenty-seven per cent of TB patients were co-infected with at least one intestinal helminth. At baseline, absolute frequencies of leucocytes, monocytes and eosinophils from TB and TB + Helm patients differed from those of healthy subjects. In comparison to either TB patients or healthy controls concomitant intestinal helminth infection showed negative impact on absolute frequencies of CD3 (+), CD4 (+), CD8 (+), natural killer (NK) T and CD4 (+) CD25 (high) T cell subsets.

Differences in CD4 (+) T cell frequencies were accompanied by lower IFN- γ and elevated and sustained interleukin (IL)-10 levels in whole blood (WB) cultures from TB + Helm compared to TB patients. In addition to depressed anti-*MTB* immunity, TB + Helm infected patients presented with more severe radiological pulmonary disease. Elias, *et al.* [5] indicated intestinal helminth infection is considered to be one of the risk factors for the development of active pulmonary TB. Resende, *et al.* [6] strengthen this idea as concomitant intestinal helminth infection in patients with newly diagnosed TB skews their cytokine profile toward Th2 responses, which could favor persistent *MTB* infection and a more protracted clinical course of the disease.

De-worming of soil transmitted helminths and *Mycobacterium tuberculosis* antigenicity

The benefits of De-worming programs throughout the world have shown significant improvement in childhood growth, physical fitness, cognition, and hemoglobin and serum ferritin concentrations. Since the public health case for de-worming has already been demonstrated by its effectiveness in enhancing the development of children, large scale eradication of helminthic infections throughout the poor world in the context of AIDS and tuberculosis epidemics is feasible and should be seriously considered and implemented, even if the consequences are only probable or partially positive. Besides, de-worming of soil transmitted helminths decrease the chance of being infected with *MTB* and its severity which might be due to the rise of TH1 immune response against the bacteria [18].

In addition, de-worming of helminth co-infected TB patients induced a significant decline in peripheral eosinophil granulocytes, and a non-significant increase in peripheral CD4+ T-cells. TB patients who received effective albendazole treatment also showed a borderline significant decrease in IL-10 levels at follow up. In patients with TB, asymptomatic helminth infection induces increased Treg response and increased levels of IL-5 and IL-10 producing peripheral blood mononuclear cells [7]. Thus, de-worming improves the immune response against *MTB* in concomitant infected patients.

The immunogenicity of BCG after de-worming helminth infected individuals

Immunomodulation and TH2-biased pre-existing immune profile caused by helminthic infections have a great impact on the host response to mycobacterial vaccination. This could be due to the shifting of TH1 immune response to TH2. Studies by Elias, *et al.* [19] showed that the efficacy of BCG against *MTB* is low in high STH prevalent geographical settings. According to Borkow, *et al.* [20] study on peripheral blood mononuclear cells, after being de-wormed the mycobacterial antigen-specific cytokine responses were significantly accelerating.

As Fine [21] indicated the efficacy of BCG is low and the incidence of TB is high in the tropics where intestinal helminths are endemic. Elias [5] also confirmed the immunogenicity of BCG as high after de-worming of helminth infected individuals. Further study was made by Elias, *et al.* [22] and strengthen that chronic worm infection reduces the immunogenicity of BCG in humans which is due to increased TGF- β production but not with enhanced Th2 immune response.

Randomized clinical trials among Ethiopian volunteers also showed de-worming improves efficacy of BCG vaccination [23]. Further investigation for the likely cause of low efficacy in BCG vaccination indicated that the presence of intestinal helminth infection and consequent impairment of immune response recall antigens. Hence, helminth infections hamper the development of adequate immune responses to vaccines like tetanus toxin and cholera vaccine [5].

Finally, several investigators have shown that immune profile induced by a given infection could have an impact on the outcome of subsequent infections or vaccinations. With the existence of soil transmitted helminthic infections the efficacy of oral administered vaccine against cholera, polio and rotavirus is affected by decreasing Seroconversion [24]. According to Borkow, *et al.* [25], infection by helminths causes chronic immune activation which leads to immune dysregulation and immunological unresponsiveness of the host to other disease.

Absence of helminth infections as a possible factor in the aetiology of immune-mediated disease

Immune-mediated diseases are those which include inflammatory bowel disease (IBD), asthma, multiple sclerosis (MS) and autoimmune (type 1) diabetes (T1D). The diseases have risk factors in less helminth prevalent areas where there is lower exposure to the helminths. Colonization with helminths alters the immune reactivity and might also promote regulatory response [26]. Clinical trials done by Summers, *et al.* [27] proved exposure to helminths can reduce immune mediated disease.

Immune-mediated diseases are rare in less-developed countries where the endemicity of helminth infection is high. Such rare immune mediated disease in helminth colonized area is not due to inability to diagnose the illnesses in less-developed settings but due to high helminth burden [26]. Contrary to their pathogenic effect, a study made by Jackson, *et al.* [28] also showed there is a high tendency of being susceptible to allergy and autoimmune disease in regions where there is less frequency of helminths.

Scrivener, *et al.* [29] reported people with *A. lumbricoides* or hookworm (*Necator*) infections had less wheezing (a sign of asthma) than people without those infections. Fleming and Cook [30] also added Multiple sclerosis is exceedingly rare where the other soil transmitted helminth (*T. trichiura*) carriage rates are greater than 10%. In contrast, Immune-mediated diseases arose in those populations where exposure to helminths declined. Such studies suggest that absence of helminth infections is a possible factor in the aetiology of immune-mediated disease. Epidemiological and animal model evidence also revealed loss of helminth exposure increases the risk of developing immune-mediated disease [31].

Therefore, there has been much interest in recent years regarding how much the presence or absence of helminth infections may interrupt on the function of our immune system. Suggestions have been made that absence of natural helminth infections in westernized countries may be associated with an increase in allergic and autoimmune disorders. On the contrary, continued presence of such helminth infections in developing countries may have a detrimental effect on vaccination and on the immune response to concurrent infectious diseases like *MTB* [32].

Recent studies on the implementation of large scale de-worming program by World Health Organization affects the immune profile of Th1/Th2. This realization leads to the higher risk of inflammatory diseases and allergies [33]. Beside those of experimental animals, some human studies also confirmed intestinal helminths modulate the occurrence of allergies and asthma [34]. The autoimmune diseases like multiple sclerosis [35] and inflammatory bowel disease are increasing due to minimization of STH infections in some developed countries [36].

Prevention and control mechanisms of STH and *MTB*

Though considerable progress has been made in the use of geographical information systems (GIS) and remote sensing (RS) to better understand helminth ecology and epidemiology there is still a problem in the control program [37]. Many studies revealed that there is a high prevalence of STH particularly in school age population with an infection rate ranging between 25% and 35% [38]. Regular use of anthelmintic drug, sanitation and personal hygiene, and health education are the major interventions in the prevention programs. The anthelmintic drug treatment should have also been used to minimize morbidity by decreasing the worm burden. Reduction of soil and water contamination using environmental sanitation minimizes the infection rate. Furthermore, encouraging health behaviors or social awareness using mass training helps to reduce transmission rate and re-infection among the society. Using combinations of these key interventions support the long-term control and elimination program. Indeed, without an improvement in sanitation and a dramatic change in defecation habits, periodic de-worming cannot attain the expected outcome [39].

On the other hand, tuberculosis is almost 100% curable and can be controlled if appropriate measures are under taken [40]. Education of community awareness, rapid accurate diagnosis under high quality laboratories, immunization with TB vaccine at childhood and correct use of drugs play major roles in the control program. Appropriate policies must be set to ensure effective clinical and public health management with committed and coordinated efforts from within and outside the health sector for the control [41].

Though studies are going on to solve the impact of tuberculosis, there is an increasing emergence of multidrug resistance and extensively drug resistance bacteria that cause major threat to effective TB control. The World Health Assembly (WHA) in 1991 considered particular attention to the disease burden when TB was recognized as a major public health problem. WHO also declared TB as a "global health emergency" in 1993 with the DOTs program development in 1994 to combat tuberculosis and minimize the disease complication

[42]. In contrast, complications of TB with HIV and emergence of drug resistant tuberculosis inhibit the achievement of the planned global STOP TB program. Hence, to accomplish the progress of TB prevention, care and control program adequate funding and collaborative work is compulsory [43].

The control of *MTB* infection requires a clearly delineated Th1 response (IL-12, IFN-g, and TNF-a) and, to a lesser extent, a Th17 response (IL-17 and IL-23). Both Th1 and Th17 responses have been shown to be important in the induction and maintenance of protective immune responses in mouse models of *MTB* infection or for control of human *MTB* infection as seen in latent tuberculosis. Moreover, *MTB* is limited within granulomas during latency period where the mycobacteria reside in macrophage that limits its growth and replication. The Maintenance of this granulomatous lesion is mediated by CD4+ and CD8+ T cells.

The influence of helminthic infections on resistance to other diseases

Chronic helminth infections not only influence immunity against TB but also other diseases of public health importance. Removal of these helminths might be important in the context of fighting other infectious and non-infectious diseases due to the rise in Th1 [5]. Different data showed helminthic infections have profound debilitating effects particularly on the immune system of the host, potentially compromising the host capacity to cope with other infections and to mount efficacious immune responses. Moreover, it might be thought that without the eradication of helminthic parasites, HIV, malaria and TB vaccines would fail to confer protection in helminth endemic areas, implying that eradication of helminthic infections, or modulation of the immune change that they cause, should be instituted prior to cure and mass vaccination of other infectious disease [44-46].

Conclusions and Future Direction

Studies on the immune profile of *MTB*-STH co-infection revealed non-conclusive tips. However, most of them agreed with STH infections as altering the Th2 immune profile production which down-regulates Th1 cells that plays a significant role against *MTB*. Furthermore, cytokines produced by Th2 particularly IL-4 acts against the production of Th1 and contrarily the pro-inflammatory cytokines IFN- γ secreted by Th1 due to infection of *MTB* interrupts Th2 production. Such cross-regulation of immune profiles could also aggravate latent TB in STH prevalent areas. Additionally, a marked suppression of both innate and adaptive immunity by the helminths makes individuals as more susceptible to other diseases. The poor immunogenicity of BCG vaccination in helminth infected population is also accompanied by enhanced TGF beta production. Other studies reviewed in this paper showed that even chronic helminth infections negatively influence immune responses against TB. Thus, consistent health education to enhance the society's awareness about tuberculosis and soil transmitted helminthiasis, proper environmental sanitation and personal hygiene, rapid accurate diagnosis, exact use of drugs and vaccination plays a remarkable role in the prevention and control program of the diseases. Furthermore, mass de-worming might also be a cost effective approach in reducing morbidity due to helminths and co-infection where malaria, tuberculosis and HIV are endemic. Lack of strong and consistent evidence for the association between STH-*MTB* co-infections desires further investigations. Further additional detailed studies are required to settle a precise knowledge of the immune profiles elicited by STH-*MTB* co-infections in endemic communities.

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